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# The pulmonologist's point of view on lung infiltrates in haematological malignancies

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## KEYWORDS

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**Abstract** In haematological malignancies, the development of lung disease is a common source of significant morbidity and mortality for this population of patients. There is a wide range of infectious and non-infectious aetiologies that can be responsible for such complications. It is a major challenge to make an early diagnosis of aetiology in order to choose the most suitable treatment. Computed tomography (CT) of the chest has undeniably become a crucial tool in diagnosing these cases of lung disease. Although it is not possible to make a definitive diagnosis of aetiology based solely on analysing CT scan findings in these complex patients, there are some abnormalities that are highly suspicious for particular diagnoses. CT, therefore, allows the clinician to put forward and prioritise possible diagnoses that may then be considered in view of clinical information and laboratory study results. There must be multidisciplinary involvement in the management of lung disease patients and there must be an ongoing dialogue between the radiologist and the clinician.

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## Abbreviations

CT	Computed tomography
HSC	Haematopoietic stem cells
CMV	Cytomegalovirus

## Introduction

It is common for lung disease to develop in patients who are being managed for malignant haematological disease. Indeed, over half of these patients present pulmonary

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abnormalities during their follow-up, and these could relate to any of a large number of both infectious and non-infectious diseases, with a significant burden of morbidity and mortality [1]. Management of these kinds of complications is challenging both in terms of diagnosis and treatment. It requires a rigorous approach that must take a number of factors into consideration, and of these, chest imaging occupies a central place. The chest CT scan is clearly established as superior to the standard chest radiograph in this context. On CT, the presence of lesions that are not visible on radiography can be confirmed and its use assists in guiding the diagnosis of aetiology when considered together with the rest of the patient data.

## Indications for chest CT

There are three main situations in which chest computed tomography is indicated:

- when haematological disease is diagnosed. This is especially so in the case of lymphoma;
- if there is a suspicious chest sign at any time during the patient's management;
- if the patient presents unexplained fever, especially if they have neutropenia or are receiving haematopoietic stem cells.

Chest CT is also useful for confirming the nature of any opacities that may have been demonstrated on chest radiography. Finally, it is crucial for guiding bronchoscopy for taking targeted samples (bronchoalveolar lavage, transbronchial needle aspiration).

## Key factors for interpreting an abnormality detected on chest CT

The management of these patients is complex due to the wide range of possible aetiologies that must be considered when a lung infiltrate is found. Because they are common and serious, infections must be the first cause to be considered as a matter of routine. However, at least a quarter of lung infiltrates presented by patients with haematological malignancies have a non-infectious cause (drug toxicity, heart failure, specific lung involvement connected to the underlying disease, intra-alveolar haemorrhage, etc.) [2]. It is nonetheless important to note that these non-infectious causes of lung disorders can coexist with an infectious aetiology.

In the same way, among the infectious causes there are numerous pathogens (bacteria, viruses, fungi, parasites) that can cause pneumonia and co-infections are common when these predisposing factors are present, making the interpretation of radiological abnormalities even more complex. This means that in this context there are a number of factors that need to be considered in order to interpret pulmonary abnormalities seen on radiology.

## Factors connected to haematological disease

### Type of haematological disease

Not every type of haematological malignancy is found with every cause of lung disease. For example, while specific involvement of the pulmonary parenchyma is common in lymphoma, it is very rare in myeloma or chronic myeloid leukaemia. Similarly, certain groups of haematological malignancy are often associated with a similar treatment profile. This means that the kind of immunosuppression seen is often similar and the risks of infection are comparable. This is the case, for example, with the widespread use of rituximab to treat lymphoid diseases, which are associated with an increased incidence of pneumococcal or haemophilus influenzae respiratory infections. Another example is the administration of fludarabine to treat chronic lymphocytic leukaemia, which leads to an increased risk of pneumocystosis. Furthermore, numerous treatments that are often prescribed for specific haematological diseases have a well-established association with potential lung toxicity ([www.pneumotox.com](http://www.pneumotox.com)): some examples are bleomycin in Hodgkin's lymphoma, cytarabine, used to treat acute leukaemias, and tyrosine kinase inhibitors in chronic myeloid leukaemia [3].

In addition, there are various non-infectious lung disorders that often complicate the course of specific haematological malignancies: some examples are sarcoid-like granulomatosis in Hodgkin's lymphoma, organising pneumonia or eosinophilic pneumonia in myelodysplastic syndromes, and amyloidosis in myeloma [4,5].

Finally, interpreting a chest CT scan is complicated by the fact that the same type of pulmonary infection can present differently depending on the underlying disease. This is the case in invasive pulmonary aspergillosis, which almost always presents as a nodule with a peripheral halo in patients on induction or consolidation treatment for an acute leukaemia, while it may have a more varied presentation in patients being treated for a lymphoid haematological disease or who have received an allogeneic HSC transplant [6].

### Stage of the haematological disease/Treatment phase

It is essential to be aware of the stage of the patient's haematological disease as well as their current treatment phase in order to be able to interpret pulmonary radiological imaging. If pulmonary opacities are identified in well-controlled haematological disease this means that a specific involvement caused by the underlying disease is unlikely. The presence of ground glass opacities together with septal thickening on a chest CT scan carried out in a patient presenting oxygen desaturation a few hours after hyperhydration in induction chemotherapy for an acute leukaemia or conditioning for an allogeneic HSC transplant means that the initial hypothesis that suggests itself is pulmonary oedema; intra-alveolar haemorrhage must be considered in a patient with significant thrombocytopenia, etc.

Allogeneic HSC transplant is a treatment phase that may well be complicated by a variety of infectious and non-infectious lung disorders [7]. Apart from the infectious lung

diseases that are very common both during the period of aplasia and during follow-up of patients receiving immunosuppressant treatment for graft versus host disease, these patients can also develop bronchiolitis obliterans, an organising pneumonia or a diffuse interstitial lung disease [7].

## Profile of immunodeficiency

The patient's profile of immunodeficiency defines the type of infectious risks that they are exposed to. It is related to the underlying haematological disease and the immunosuppressant treatments received, and it depends on the predicted duration and extent of immunosuppression:

- arnulocytosis and/or granulocyte disorders, often present during chemotherapy;
- antibody-mediated immunity deficiency, which is expressed as hypogammaglobulinemia and is often found in chronic lymphocytic leukaemias, myelomas, HSC transplants, and treatment with anti-CD20 antibodies;
- cell-mediated immunity deficiency, which is associated with long-term corticosteroid use, treatment with anti-CD52 antibodies or purine analogues, HSC transplants, and lymphoproliferative disorders;
- spleen dysfunction secondary to a splenectomy, or splenic or total body irradiation.

These different immunosuppression profiles often arise in the same patient at different stages in the management of their haematological malignancy and this complicates the assessment of each patient.

Each immunosuppression profile is connected with a particular vulnerability to one pathogen or another. For example, pneumococcal or *Haemophilus influenzae* pneumonias are especially common in patients who have an antibody-mediated immunity deficiency; lung diseases caused by bacteria may be the most common type found in patients with neutropenia, but an invasive fungal infection will be routinely considered in prolonged neutropenia, and pneumocystosis or community-acquired viral lung diseases are common in patients with a deficiency in cell-mediated immunity.

## Treatments for infection received

If a patient presents a fever or a suspicious pulmonary sign, those on treatment for a haematological malignancy will urgently receive a broad-spectrum empirical treatment for infection in view of their immunodeficiency, often before a chest CT scan has been carried out. In parallel, there are a number of prophylactic or pre-emptive treatments they may receive. These treatments must be taken into account when abnormalities seen on the CT scan are being interpreted.

Empirical treatment is largely applicable during periods of febrile neutropenia and consists of broad-spectrum antibiotics effective against Gram-negative bacilli (including *Pseudomonas*, often responsible for lung disorders in these circumstances) and Gram-positive cocci. If fever persists beyond, 72 hours an anti-fungal treatment will be added.

Prophylactic treatment consists of administering anti-infective agents to a whole population of patients in order to reduce the risk of infection in this population. The most

effective prophylaxis is trimethoprim/sulfamethoxazole, which makes a diagnosis of pneumocystosis very unlikely. If a patient presents spleen dysfunction, this justifies the use of anti-pneumococcal prophylaxis in order to limit the risk of pneumococcal lung disorders. Patients with aplasia after chemotherapy for leukaemia or who have been treated for graft versus host disease after an allogeneic HSC transplant can be given anti-fungal prophylaxis that is effective against *Aspergillus*.

Pre-emptive therapy involves routinely and repeatedly using microbiology screening techniques in order to treat a patient at risk before they develop clinical symptoms. One example of this is the practice of routinely performing peripheral blood PCR to screen for CMV in allogeneic HSC transplant recipients, with antiviral treatment starting as soon as there is an increased viral load. This has led to a considerable reduction in the incidence of CMV pneumonia in this population. Indeed, during the 1980s the incidence of CMV pneumonia in allogeneic HSC transplant recipients was greater than 30%, and today it is estimated at 5% [8,9].

Nonetheless, clinicians must remain vigilant, especially after these preventive treatments have been stopped because immunosuppression can persist or reappear.

## Patient history

The background against which radiological abnormalities have been found, as well as the way in which any respiratory symptoms have set in, needs to be incorporated into the interpretation that is made of the chest CT scan. The finding of centrilobular micronodules in a patient who has developed a debilitating dry cough and fever a few days after exposure to a contagion during an epidemic of community-acquired respiratory virus, makes the diagnosis of community-acquired viral pneumonia very likely. In the same way, the geographic origin of a patient or any previous exposure to tuberculosis becomes important when interpreting the finding of necrotic mediastinal lymphadenopathy, irrespective of what the underlying haematological disease is. It is significant if the patient uses tobacco when a pulmonary nodule is found, especially in a haematological disease that is associated with an increased risk of cancers, such as chronic lymphocytic leukaemia.

## Clinical signs

Apart from fever, which is suggestive of an infectious cause of lung disease, respiratory clinical signs add very little in terms of pointing towards a specific aetiology. This means that, for example, even though chest pain and haemoptysis are often associated with invasive pulmonary aspergillosis, these symptoms are often absent and they can be found in other situations, so they are not specific. It is rare to see signs elsewhere in the body, but these can be extremely useful for diagnosis. For example, the combination of cerebral involvement and a lung infiltrate will point to a mycobacterial infection, toxoplasmosis, fungal infection, or nocardiosis. Cutaneous involvement may be suggestive of mycosis (candidiasis, fusariosis, aspergillosis)

or nocardiosis. Sinus involvement may point to mycosis (aspergillosis, mucormycosis).

## Analysing CT scan abnormalities

The chest CT scan has become the key investigation for diagnosing lung disease in haematology patients. The current question is one of determining how useful CT is in terms of pinpointing the aetiology of lung involvement in this context. There are several approaches that can contribute answers to this problem:

- the description of the most decisive CT scan abnormalities that are present in small groups of patients with an identified lung disorder; this applies for example to the centrilobular micronodules that are almost always found in patients with a lung disease caused by the Parainfluenzae virus [10] or the nodule with a halo sign in neutropenic leukaemia patients [11];
- studies into the correlation between CT features and pulmonary histology findings that allow, for example, a description to be made of the unique CT features of organising pneumonia in patients who have undergone allogeneic HSC transplant [12] or those of invasive pulmonary aspergillosis in view of the underlying predisposing factors [13–15]. These studies promote both an anatomical and pathophysiological reading of the CT scan, which is very helpful in these complex patients. Taken as such, centrilobular micronodules are suggestive of a pathology targeting bronchiolar tissue such as community-acquired viral infections, invasive aspergillosis in allogeneic HSC transplant recipients, or bronchiolitis caused by *Haemophilus*. In the same way, septal thickening, for example, points to a pathology of the lymphatic system: lymphangitis, pulmonary oedema, etc.;
- other studies have attempted to associate specific CT scan features with a given pathogen. For example, it has been suggested that bacterial pneumonia is usually demonstrated as alveolar consolidation, that fungal lung disease presents as nodules in 90% of cases, nearly half of which are thought to be cavitated, and that pneumocystosis is associated with ground glass opacities in 100% of cases [16].

However, there is no CT scan feature that is pathognomonic for a particular pathogen and CT alone is therefore not enough to make a microbiological or histological diagnosis. This is even more the case in view of recent data suggesting that CT features of a given infectious pneumonia differ depending on the patient's underlying predisposing factors. For example, while the halo sign is almost always seen in invasive pulmonary aspergillosis in patients with neutropenia being treated for acute leukaemia, it is less often present in the wider population of haematology patients [17]. Moreover, whether the halo sign or cavitated nodules in aspergillosis are found depends on how early the diagnosis is being made. While the halo sign appears early and transiently, cavitation develops later [11]. Finally, although the nodule with a halo may be strongly associated with the diagnosis of invasive aspergillosis, it can also be one characteristic of other less common and emerging invasive fungal lung diseases [18].

## Microbiology and histology tools

The CT scan is carried out at an increasingly early stage for the investigation of lung disease in haematology patients and it is almost always done before a bronchoscopy and of course before a lung biopsy. Apart from when the chest CT scan is indicated to investigate a positive *Aspergillus* antigen test as part of routine monitoring, microbiology and histology results are not usually available before the CT scan has been carried out and this means that they must be considered later in the interpretation of the radiological findings in a given patient. Nonetheless, in addition to their value for individual patients, they are very useful in furthering our understanding of opacities found on CT scans. For example, progress that has been made in molecular biology has meant that numerous community-acquired respiratory viruses causing lung disease in haematology patients can be identified and their incidence determined (metapneumovirus, parainfluenzae virus, etc.) [10,19].

## Conclusion

The chest CT scan has undeniably become a crucial aspect in the diagnosis of lung disease in patients being managed for haematological malignancies. Although it may not be possible to make a definitive diagnosis of aetiology based solely on analysing CT scan findings in these complex patients, there are some abnormalities that are highly suggestive for particular diagnoses. CT must therefore allow the clinician to put forward and prioritise possible diagnoses that may then be considered in view of clinical information and laboratory study results. There must be multidisciplinary involvement in the management of these lung disease patients and there must be an ongoing dialogue between the radiologist and the clinician as soon as any new data is discovered.

## Disclosure of interest

The author declares that she has no conflicts of interest concerning to this article.

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